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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,085	04/16/2007	Koji Sode	3691-0130PUS1	8739

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
06/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/574,085	SODE, KOJI	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I (claims 1-8) with traverse in the reply filed on 04/26/2010 is acknowledged.

The traversal is the grounds that "Unity of invention exists when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. Although lack of unity of invention should certainly be raised in clear cases, it should neither be raised nor maintained on the basis of a narrow, literal or academic approach. There should be a broad, practical consideration of the degree of interdependence of the alternatives presented. If, there is a single general inventive concept that appears novel and involves inventive step, then there is unity of invention and an objection of lack of unity does not arise. For determining the action to be taken by the examiner, rind rules cannot be given and each case should be considered on its merits, the benefit of any doubt being given to the applicant, see MPEP § 1850 II."

Applicants further argue that "In the present instance, Group I, Group II, and Group III are closely related. Group I claims are directed to fusion proteins having the acknowledged special technical features, see Office Action, page 2. Group II claims are directed to the fusion proteins and genes, vectors and transformants for producing the recited fusion proteins. Group III claims are directed to the fusion proteins and enzyme electrodes comprising the recited fusion proteins. Accordingly, Applicants submit that the general inventive concept of the fusion proteins described in Group I should be considered with the genes, vectors, and transformants for producing such proteins and the enzyme electrodes comprising the recited proteins. As such, Applicants request rejoinder of Groups I-III."

Applicants arguments are considered but not found to be persuasive because "The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature for the following reasons: The technical feature linking Groups I-III appears to be that they all relate to fusion protein of SEQ ID NO: 2 (fusion between cytochrome with the C-terminal end of PQQGDH from *Acinetobacter*

calcoaceticus). According to the international preliminary examination report [IPER] clams 1-6 & 9-15 lack novelty as being obvious over Document 1 [WO 02/073181 A (9/19/2002), Koji Hayade] and Document 2 [JP 2002-125689 A (5/8/2002), Koji Hayade]. Further, claims 7-15, being obvious over Documents 1, 2 & 3.

The teachings and conclusions of the ISR are reproduced here for convenience.

Document 1 describes that (1) pyrroloquinolinequinone glucose dehydrogenase derived from Acinetobacter calcoaceticus and (2) cytochrome b562, both of which were chemically bridged each other, were used as a glucose sensor to measure glucose.

Document 2 describes that fused protein obtained by *fusion* of (I) pyrroloquinolinequinone glucose dehydrogenase derived from Acinetobacter calcoaceticus and (2) a biotin bound portion was used as a glucose sensor to measure glucose.

Regarding claims 1-6, and 9-15, a person skilled in the art could have easily arrived at using fused protein, as described in document 2, in combining (1) pyrroloquinolinequinone glucose dehydrogenase derived from Acinetobacter calcoaceticus and (2) cytochrome b562, both of which are described in document 1.

The inventions described in claims 7-15 do not appear to involve an inventive step in view of documents 1-3 cited in the ISR.

Document 3 describes that cytochrome B562 derived from *Comamonas testeroni* has a function as an electron acceptor of pyrroloquinolinequinone glucose dehydrogenase.

Regarding claims 7-15, a person skilled in the art could have easily arrived at using cytochrome B562 derived from *Comamonas testeroni* described in document 3, as cytochrome B562.

Therefore, Groups I-III share no special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

Further Group I & II claims are broadly drawn to any combination of innumerable fusion proteins comprising pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) and a cytochrome from any source or genes encoding the said construct; as well as the specific fusion construct of the amino acid sequence of SEQ ID NO: 2 or

the encoding nucleic acid of SEQ ID NO: 2; for which the searches have to be performed in different data bases including various patent, non-patent as well as various sequence search in protein and nucleic acid sequence data bases. Searching for a single group will not necessarily gather art of the other groups; or search for fusion protein sequence will not necessarily gather art for the nucleic acid encoding the protein. The distinct groups and distinct sequences will require additional searching which would be undue burden to the Examiner. The requirement is still deemed proper and is therefore made FINAL.

Art rejections are described in detail in this Office Action.

2. Claims withdrawn:

Claims 9-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. ***Priority***

Applicant's claim for domestic priority under 35 U.S.C. 119(e), filed 039/30/2003, is acknowledged.

4. ***Drawings***

The drawings filed on 3/30/2006 are acknowledged.

5. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

6. Claims 1-8 drawn to a fusion protein of pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) and a cytochrome (SEQ ID NO: 2) are under consideration.

7. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-8 are broadly drawn to a fusion protein of pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) and a cytochrome (claim 1), the claimed genus. Dependent claims 2-8 drawn to a fusion protein of claim 1, wherein the PQQGDH is a water-soluble PQQGDH derived from *Acinetobacter calcoaceticus* (claim 2); or wherein the cytochrome has been fused to the C-terminal side of PQQGDH (claim 3); or wherein the cytochrome is cytochrome c or cytochrome B562 (claim 4); or wherein the cytochrome is derived from a quinohemoprotein which is a protein having both PQQ and a heme in one molecule (claim 5); or wherein the cytochrome is derived from a quinohemoprotein alcohol dehydrogenase (claim 6); or wherein the cytochrome is derived from quinohemoprotein ethanol dehydrogenase from *Comamonas testosterone* (claim 7); or the fusion protein of claim 1, wherein (a) a protein comprising an amino acid sequence represented by SEQ ID NO: 2; or (b) a protein comprising an amino acid sequence in which one or more amino acid residues have been deleted, substituted or added in the amino acid sequence (a) and having a glucose dehydrogenase activity and an electron transfer ability (claim 8).

The specification, however, only provides description of a single species of DNA (SEQ ID NO: 1) encoding the fusion protein of SEQ ID NO: 2 for direct electron transfer-type glucose sensor for measuring blood glucose level.

The specification does not contain any disclosure or description of the structure and function of all fusion protein constructs comprising pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) and a cytochrome from any source or from specific source with no defined structure or a fusion protein construct wherein the protein comprising an amino acid sequence, in which one or more amino acid residues have been deleted, substituted or added in the amino acid sequence of SEQ ID NO: 2 and having a glucose dehydrogenase activity and an electron transfer ability. The single species disclosed (SEQ ID NO: 2) is not representative of the genus claimed. According to MPEP 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V.*

v.Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed.Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

The scope of each genus includes many members of fusion construct with widely differing structural, chemical, and physical characteristics. Furthermore, each genus is highly variable because a significant number of structural differences between genus members exit. The specification does not describe and define any structural features and amino acid sequences commonly possessed by each genus. There is no art-recognized correlation between any structure of a fusion protein and the sequence of SEQ ID NO: 2 and wherein such fusion proteins have the desired glucose dehydrogenase activity and an electron transfer ability. Those of ordinary skill in the art would not be able to identify without further testing what specific DNA sequences that can be prepared and would encode the desired fusion protein having glucose dehydrogenase activity and an electron transfer ability.

The genus of fusion protein may be obtained with the aid of a computer by a skilled artisan. However, there is no teaching regarding how the sequences obtained from different sources can be fused recombinantly that can be varied and fused and still result in a DNA encoding a protein having glucose dehydrogenase activity and an electron transfer ability. An important consideration is that structure is nor necessarily a reliable indicator of function. The instant specification provides no disclosure relating similarity or identity of structure to conservation of function. General knowledge in the art provides guidance to modification of some amino acids that are tolerated without losing a protein's tertiary structure. An important consideration is that structure is not necessarily a reliable indicator of function. In this example, there is no disclosure relating similarity of structure to conservation of function. General knowledge in the art included the knowledge that some amino acid variations are tolerated without losing a protein's tertiary structure. The results of amino acid substitutions have been studied so extensively that amino acids are grouped in so-called "exchange groups" of similar properties because substituting within the exchange group is expected to conserve the overall structure. For example, the expectation from replacing leucine with isoleucine would be that the protein would likely retain its tertiary structure. On the other hand,

when non-exchange group members are substituted, e.g., proline for tryptophan, the expectation would be that the substitution would not likely conserve the protein's tertiary structure. Given what is known in the art about the likely outcome of substitutions on structure, those in the art would have likely expected the applicant to have been in possession of a genus of proteins having a tertiary structure similar to SEQ ID NO: 2 although the claim is not so limited. However, conservation of structure is not necessarily a surrogate for conservation of function. In this case, there is no disclosed correlation between structure and function. There is no disclosure of the active site amino acid residues responsible for the catalytic activity. While general knowledge in the art may have allowed one of skill in the art to identify other proteins expected to have the same or similar tertiary structure, in this case there is no general knowledge in the art about similar proteins to SEQ ID NO: 2 to suggest that general similarity of structure confers the activity. Accordingly, one of skill in the art would not accept the disclosure of SEQ ID NO: 2 (or the encoding DNA of SEQ ID NO: 1) as representative of other proteins having glucose dehydrogenase activity and an electron transfer ability. The specification, taken with the pre-existing knowledge in the art of amino acid substitution and the genetic code, fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

8. ***Claim Rejections - 35 USC § 112, first paragraph (Enablement)***

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a fusion protein of SEQ ID NO: 2 for direct electron transfer-type glucose sensor for measuring blood glucose level, does not reasonably provide enablement for all fusion protein constructs comprising pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) and a cytochrome from any source or from specific source with no defined structure or a fusion protein construct wherein the protein comprising an amino acid sequence, in which one or more amino acid residues have been deleted, substituted or added in the amino acid sequence of SEQ ID NO: 2 and having a glucose dehydrogenase activity and an electron transfer ability. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of fusion constructs comprising individual elements of fusion constructs various modified and broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequence of SEQ ID NO: 1 and encoded amino acid sequence of fusion protein of SEQ ID NO: 2, having a glucose dehydrogenase activity and an electron transfer ability. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass obtaining any fusion protein comprising PQQGDH and a cytochrome from any source or wherein the fusion protein is variously modified by modifying the protein/DNA sequence to any extent by insertion, deletion or substitution, and encoding or retaining the glucose dehydrogenase activity and electron transfer ability, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting fusion protein activity; (B) the general tolerance of fusion protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any fusion protein residues with an expectation of obtaining the

desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including fusion protein constructs with an enormous number of nucleic acid/amino acid modifications of the sequence(s) of SEQ ID NO: 1/2 [as a result of modifying the DNA]. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the numerous fusion protein constructs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

9. ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koji Hayade [WO 02/073181 A (9/19/2002)] **or** Sode, Koji [PrePub document No.

20050067278, 3/13/2001), Koji Hayade [JP 2002-125689 A (5/8/2002), Document 2], and Oubrie et al. [JBC 277(5): 3727-3732 (2002)]

The teachings and conclusions of the ISR are reproduced here for convenience.

Koji Hayade [WO 02/073181 A (9/19/2002), cited in IDS], describes that (1) pyrroloquinolinequinone glucose dehydrogenase derived from *Acinetobacter calcoaceticus* and (2) cytochrome b562, both of which were chemically bridged and were used as a glucose sensor to measure glucose. The reference does not teach the combining glucose dehydrogenase and cytochrome by recombinant means in order to obtain a fusion protein.

Sode, Koji [PrePub document No. 20050067278, 3/13/2001), teach chemical cross-linking of glucose dehydrogenase (an oxidoreductase) and the electron-transfer protein is cytochrome c or cytochrome b562, an enzyme electrode (and/or a sensor) comprising the cross-linked enzyme/cytochrome for monitoring glucose levels. Paragraph 0032-0035 teach recombinant means of producing water-soluble PQQGDH and b562 in *Escherichia coli*. The reference does not teach the combining glucose dehydrogenase and cytochrome by recombinant means in order to obtain a fusion protein.

Koji Hayade [JP 2002-125689 A (5/8/2002), cited in IDS], describes that fused protein obtained by *fusion* of (I) pyrroloquinolinequinone glucose dehydrogenase derived from Acinetobacter calcoaceticus and (2) a biotin bound portion was used as a glucose sensor to measure glucose. The reference does not teach the combining glucose dehydrogenase and cytochrome by recombinant means in order to obtain a fusion protein.

Oubrie et al. [JBC 277(5): 3727-3732 (2002), cited in IDS] describes that cytochrome B562 derived from *Comamonas testeroni* has a function as an electron acceptor of pyrroloquinolinequinone glucose dehydrogenase. X-ray structure of the quinohemoprotein alcohol dehydrogenase from *Comamonas testosteroni* has been determined at 1.44 A resolution. It comprises two domains. The N-terminal domain has a β-propeller fold and binds one pyrrolo-quinoline quinone cofactor and one calcium ion

in the active site. The reference does not teach the combining glucose dehydrogenase and cytochrome by recombinant means in order to obtain a fusion protein.

It would have been obvious for one of ordinary skill in the art following the teachings of Koji Hayade [WO 02/073181 A (9/19/2002)] and/or Sode, Koji [PrePub document No. 20050067278, 3/13/2001) of chemically combining the pyrroloquinolinequinone glucose dehydrogenase (PQQGDH) (from *Comamonas testeroni* or *Acinetobacter calcoaceticus*) and cytochrome to suitably express the combination by recombinant means in order to obtain a fusion protein of PQQGDH and cytochrome. This may be easily accomplished by substituting the biotin in Koji Hayade [JP 2002-125689 A (5/8/2002)] fusion protein with cytochrome C or 562 and do so with a reasonable expectation of success. One of ordinary skill in the art would have been motivated in view of the importance of the fusion construct in the health care industry wherein the enzyme(s) either chemically coupled or obtained as a fusion protein may then be attached to an electrode as well as a biosensor using the electrode are useful as glucose sensors for measuring blood glucose levels, for example. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, *prima facie* obvious.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached between 8.30 am - 5.00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on (571) 272 0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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